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Role of calreticulin and its deregulation in myeloproliferative neoplasms

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Mutations in calreticulin (*CALR*) were recently identified in essential thrombocythemia (ET) and primary myelofibrosis (PMF). They occur mutually exclusive with mutations in *JAK2* or in the thrombopoietin receptor *MPL*.[1,2] A 52 bp deletion (type 1) and a 5 bp insertion (type 2) were the most common alterations.[1,2] Calreticulin is mainly recognized as a chaperone in the endoplasmic reticulum, but a variety of additional functions have been attributed to the protein.[3] Patients with *CALR* mutations have significantly higher platelet counts and lower leukocyte counts than those with *JAK2* mutations.[1,2,4-6] Overall survival appears to be similar between *JAK2* and *CALR* patients in ET[4-6] whereas PMF patients with *CALR* mutations show significantly better survival.[2,7] In ET, the incidence of thrombosis is lower in patients with the *CALR* mutation.[2,4,5] Comparing *CALR* mutation types, type 1 mutations are seen at a higher frequency in PMF and are associated with an increased risk of progression to myelofibrosis in ET.[8-10] Type 2 mutations seem to cause an indolent disease course in ET,[8] whereas in PMF, they are associated with worse overall survival.[11] All these studies were performed retrospectively. There are no prospective studies published yet, that would be needed for precise estimation of the prognostic impact of *CALR* mutations. In cell line models, mutant CALR was shown to bind to MPL, what was associated with activation of the receptor, elevated JAK-STAT signalling, and cytokine independent cell growth.[12-14] In a retroviral mouse model, *CALR* mutations were shown to produce thrombocytosis and myelofibrosis, suggesting that mutant *CALR* alone is sufficient to cause an MPN phaenotype.[15] This study also showed the requirement of *MPL* expression for the development of the disease phenotype.[15]

References

*1. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med. 2013;369:2391-405.

This is one of the two original publications reporting the identification of CALR mutations in MPN.

*2. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369:2379-90.

The other publication on the original identification of CALR mutations in MPN.

*3. Michalak M, Groenendyk J, Szabo E. A multi-process calcium-buffering chaperone of the endoplasmic reticulum. Biochem J. 2009;417:651-66.

A comprehensive review on calreticulin structure and function.

4. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123:1544-51.

5. Rotunno G, Mannarelli C, Guglielmelli P, et al. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. Blood. 2014;123:1552-5.

6. Tefferi A, Wassie EA, Lasho TL, et al. Calreticulin mutations and long-term survival in essential thrombocythemia. Leukemia. 2014;28:2300-3.

7. Tefferi A, Lasho TL, Finke CM, et al. CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. Leukemia. 2014;28:1472-7.

*8. Pietra D, Rumi E, Ferretti VV, et al. Differential clinical effects of different mutation subtypes in CALR-mutant myeloproliferative neoplasms. Leukemia. 2016;30:431-8.

A comparative study on the influence of CALR type 1, type 2 and JAK2 mutations on clinical parameters in ET and PMF.

9. Cabagnols X, Defour JP, Ugo V, et al. Differential association of calreticulin type 1 and type 2 mutations with myelofibrosis and essential thrombocytemia: relevance for disease evolution. Leukemia. 2015;29:249-52.

10. Tefferi A, Wassie EA, Guglielmelli P, et al. Type 1 versus type 2 calreticulin mutations in essential thrombocythemia: a collaborative study of 1027 patients. Am J Hematol. 2014;89:E121-4.

11. Tefferi A, Lasho TL, Tischer A, et al. The prognostic advantage of calreticulin mutations in myelofibrosis might be confined to type 1 or type 1-like CALR variants. Blood. 2014;124:2465-6.

12. Elf S, Abdelfattah NS, Chen E, et al. Mutant calreticulin requires both its mutant C-terminus and the thrombopoietin receptor for oncogenic transformation. Cancer Discov. 2016;6:368-81.

13. Chachoua I, Pecquet C, El-Khoury M, et al. Thrombopoietin receptor activation by myeloproliferative neoplasm associated calreticulin mutants. Blood. 2016;127:1325-35.

14. Araki M, Yang Y, Masubuchi N, et al. Activation of the thrombopoietin receptor by mutant calreticulin in CALR-mutant myeloproliferative neoplasms. Blood. 2016;127:1307-16.

*15. Marty C, Pecquet C, Nivarthi H, et al. Calreticulin mutants in mice induce an MPL-dependent thrombocytosis with frequent progression to myelofibrosis. Blood. 2016;127:1317-24.

The first report of a retroviral mouse model for mutant CALR pathogenesis.